UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,921	02/17/2004	Frank L. Meyskens JR.	UCIVN-058C	1912

7590 07/18/2007

STOUT, UXA, BUYAN & MULLINS, LLP
Suite # 310
4 Venture
Irvine, CA 92618

EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,921	MEYSKENS ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-20* is/are rejected.

7)☒ Claim(s) *1 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-4 & 6-20 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/27/2007 has been received and entered into the application. Accordingly, claims 1-4 and 6-20 have been amended and claim 5 has been cancelled.

In view of the above amendments, the rejection of claim 6 under 35 U.S.C. 112, 2nd Paragraph has been overcome and thus is *withdrawn*. Also, the amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous office action. Such rejections are hereby withdrawn. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Priority

Receipt is acknowledged of Applicant's petition under 37 C.F.R. § 1.137(b) to revive U.S. Application No. 09/938,846 in order to establish co-pendency with the present application. Said petition was **GRANTED** on 5/17/2007. Accordingly, continuity of the instant application to U.S. Provisional Application No. 60/227,714, filed 8/24/2000, has been established.

The earliest effective U.S. filing date afforded the instant claims is 8/24/2000.

Claim Objections

Claim 1 is objected to because of the following informalities: the word "α-ifluoromethylornithine" is misspelled in line 4. The correct spelling is ---α-difluoromethylornithine--- as found elsewhere in the specification. Appropriate correction is required.

Claim 6 is objected to because of the following informalities: the abbreviation "DFSO" is misspelled in line 2. The correct spelling is ---DMFO--- as found elsewhere in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-4 and 6-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weis *et al.* (WO 98/25603) (previously cited) in view of Maierhofer *et al.* (U.S. Patent No. 5,853,753; Issued Dec. 29, 1998) (newly cited).

The instant claims, as amended, recite a method of treating prostate cancer comprising administering a lyposomal preparation of α-difluoromethylornithine (DMFO) in an amount sufficient to decrease the spermine and/or spermidine levels in the prostate.

Weis *et al.* disclose the use of single enantiomers of DMFO to prevent/treat cancers and their metastases, including prostate cancer, in humans (page 13, lines 15-32 and page 14, line 6). With respect to the "at least 90% by weight of the D isomer of DFSO [*sic*]" as recited in instant claim 6, Weis *et al.* teach a ratio of (+)-DMFO to (-)-DMFO of about 10:90 by weight (page 9, lines 5-8), thus meeting the claimed limitation. Administration is by a variety of dosage forms, including oral and intravenous (page 17, lines 19-26). The preferred dosage range of 0.5 to 3.0 g/m^2/day (page 23, last paragraph) is the same as that used by the Applicants (compare with instant claims 14-19). Treatment is specified for a period of 1 to 365 days (page 14, line 22), but may be continued as long as necessary (page 14, line 26) thus teaching the limitations of instant claims 7-10. The duration of administration recited in instant claims 11-13 (*i.e.*, 10 years, 20 years and 40 years) would have been *prima facie* obvious in view of Weis *et al.* disclosure of "as long as necessary". Further, when used for prevention, administration may be chronic, *i.e.*, indefinite for as long as required (page 23, line 20). The prior art treatment results in a reduction of polyamine levels, including putrescine, spermidine and spermine (page 1, lines 27-30 and Tables 1-3 at pages 40-42) thus meeting the limitations of instant claim 1. Levels can further be reduced effectively to zero, *i.e.* to an undetectable level (page 1, line 28).

Weis *et al.* is not anticipatory under 35 U.S.C. § 102 because prostate cancer must be selected from a relatively large list of diverse alternative cancers provided at page 13, lines 15-21 of the prior art. This is reinforced by the fact that prostate cancer is not exemplified in the form of a discrete preferred embodiment, such as a working example (*e.g.*, the prior art working examples exemplify only melanoma and leukemia at pages 37-38). However, it would most certainly have been obvious to treat prostate cancer, motivated by the prior art's specific

disclosure of that specie and its clear invitation to select alternatives. Further, Weis *et al.* do not disclose administration of DMFO in a lyposomal preparation as instantly claimed.

However, Maierhofer *et al.* is provided as evidence that liposomal preparation of drugs was well known in the art at the time of the invention (col. 1, lines 22-42). Methods of incorporating medicinal agents into liposomal preparations are also described (*id.* at lines 33-36).

Thus, in the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed method of treating prostate cancer with a liposomal preparation of DMFO would have *prima facie* obvious at the time of the invention. Weis *et al.* clearly suggest and motivate the optimization of therapeutic parameters, *e.g.*, varying the course and duration of administration, as well as dosage, depending on the particular patients being treated and the severity of their cancers (page 23, lines 15-20). Accordingly, the various instant recitations of particular durations (claims 11-14) and dosages (claims 14-19) would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Further, liposomal delivery of active agents was well known in the art as evidenced by Maierhofer *et al.* Accordingly, and in view of the broad recitation of various dosage forms of DMFO in Weis *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that DMFO could be effectively administered as a liposomal preparation.

Claims 1-4 and 6-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bey *et al.* (U.S. Patent No. 5,614,557; Issued Mar. 25, 1997) in view of Maierhofer *et al.* (U.S. Patent No. 5,853,753; Issued Dec. 29, 1998).

Bey *et al.* disclose the use of α-difluoromethylornithine (DMFO) and derivatives thereof in the treatment of neoplastic diseases (Abstract). Preferred compounds of the invention include α-DMFO, whose use is further intended as both a racemic mixture or "as individual active enantiomers" (col. 2, lines 36-46). The compounds of the invention are disclosed to produce irreversible inhibition of ornithine decarboxylase (ODC), the enzyme that catalyzes the decarboxylation of ornithine to putrescine (*id.* at lines 47-50). Such decarboxylation is the first step in the biosynthesis of the polyamines spermidine and spermine (*id.* at lines 50-52). Accordingly, Bey *et al.* contemplate that blockade of the conversion of ornithine to putrescine, such as by inhibition of ODC, can provide a method for regulating the cellular levels of the polyamines (*id.* at lines 59-63). The motivation to administer DMFO to treat tumors is disclosed at column 3, lines 9-18, wherein Bey *et al.* teach that the rapid proliferation of tumor tissue is marked by an abnormal elevation of polyamine levels. As such, the inventors believe that the compounds of the invention exert their therapeutic effect by "blocking formation of the polyamines" (*id.* at lines 12-15). The treatment of prostate tumors is explicitly disclosed (col. 3, line 38). Treatment with a compound of the invention (*e.g.*, DMFO) for 1 to 14 days is disclosed (col. 4, lines 59-60), as is treatment for 1 to 365 days following administration of a second therapeutic agent (id. at lines 63-65). Various modes of administration are contemplated, including oral and parenteral (col. 5, lines 57-66). Injection directly into a tumor as recited in claim 2 is disclosed at column 5, lines 65-66. Doses that read on the instantly claimed doses are recited. For example, 1 mg/kg to 2,000 mg/kg per day, preferably 10 mg/kg to 500 mg/kg per day, are explicitly disclosed (col. 6, lines 5-12). Injectable dosages of a "solution or suspension" of the compound in a physiologically acceptable diluent with a pharmaceutical carrier (including

water and oils) are disclosed (*id.* at lines 29-42). The reference does not explicitly recite administration of DMFO in a liposomal preparation.

However, Maierhofer *et al.* is provided as evidence that liposomal preparation of drugs was well known in the art at the time of the invention (col. 1, lines 22-42). Methods of incorporating medicinal agents into liposomal preparations are also described (*id.* at lines 33-36).

Thus, in the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed method of treating prostate cancer with a liposomal preparation of DMFO would have *prima facie* obvious at the time of the invention. Bey *et al.* clearly suggest and motivate the optimization of therapeutic parameters, *e.g.*, varying the course and duration of administration, as well as dosage, depending on the particular patients being treated and the type of cancer being treated. Accordingly, the various instant recitations of particular durations (claims 11-14) and dosages (claims 14-19) would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and amount to routine optimization of the prior art methods. Further, liposomal delivery of active agents was well known in the art as evidenced by Maierhofer *et al.* Accordingly, and in view of the broad recitation of various dosage forms of DMFO in Bey *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that DMFO could be effectively administered as a liposomal preparation for the treatment of prostate cancer.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

July 10, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER